RESPONSE UNDER 37 C.F.R. §1.116

This response is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b). This response was not presented earlier because applicants believed, and still believe, that the response filed on January 15, 2004, overcame all outstanding issues. The response should be entered because it places the application in better form for allowance or appeal, and the response does not require further searching or present any new issues.

THE FINAL REJECTION IS IMPROPER AND SHOULD BE WITHDRAWN

Applicants respectfully submit that the final rejection is not proper in this case because the examiner has raised a new ground of rejection in addition to the rejection stated on Paper No. 5. The examiner states in this Office Action (FINAL) that there is no showing of similar efficacy comparing 20 mg of the compound of the instant method with the 50 mg disclosed in Daugan U.S. Patent No. 6,140,329. The examiner did not specifically raise this ground of rejection in the previous Office Action, and it is not clear that this ground of rejection is solely based on the currently outstanding rejection under 35 U.S.C. §103. Because the rejection on the above basis is new, applicants have not been given an opportunity to present the arguments to overcome and/or traverse the rejection on this ground. In view of the above, applicants submit that a new ground of rejection has been raised in this Office Action (FINAL), which was not previously stated in the

Paper No. 5. Accordingly, applicants respectfully request that the final rejection be withdrawn.

SUMMARY OF THE INVENTION

The present invention and all pending claims are directed to a method of treating sexual dysfunction in a patient by orally administering a unit dose containing about 1 to about 20 mg of a compound (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3, 4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione) (also referred to as Compound (I)) up to a maximum total dose of 20 mg per day. See, for example, page 5, lines 10-30 of the specification. The sexual dysfunction includes, but is not limited to, male erectile dysfunction (ED) (claim 11) and female arousal disorder (FAD) (claim 12).

ISSUE

Whether claims 11-17 and 20-24 are patentable under 35 U.S.C. §103 over Daugan U.S. Patent No. 6,140,329.

ARGUMENTS

The present invention is not obvious over Daugan et al. (U.S. Patent No. 6,140,329) under 35 U.S.C. §103.

Briefly, U.S. Patent No. 6,140,329 (hereafter '329 patent) discloses a broad range of dosing relating to Compound A and B. Specifically, the '329 patent discloses: "in particular compounds A and B will generally be in the range of from 0.5-800 mg for an aver-

age adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.2-400 mg of active compound." (Column 3 lines 48-55.)

In this case, the '329 patent gives neither an indication of which parameters are critical nor a direction as to which of many possible choices is likely to be successful. See *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). In other words, the '329 patent generally discloses the broad range and nothing more.

Surprising and Unexpected Results of the Present Invention

The present invention as a whole would not have been obvious over '329 patent because the present invention has surprising and unexpected results as discussed below.

An applicant may overcome the rejection under §103 by establishing "that the claimed range is critical" generally by showing that the claimed range achieves results relative to the prior art range. *In re Geisler*, 43 U.S.P.Q.2d 1362, 1365 (Fed. Cir. July 7, 1997). The unit dose range of about 1 to about 20 mg as claimed in claim 13 is critical because this dose range exhibits the surprising and unexpected results of low adverse side effects *and* still being unexpectedly efficacious in treating sexual dysfunction. The present specification discloses the combined clinical studies as illustrated in Table of IIEF (page 31), which shows the efficacy of the compound at a dosing range of 2-100 mg. It is worth noting from this table that the lower doses are found to be efficacious. The

present specification also discloses that doses at a higher level (i.e., above 20 mg), although efficacious, result in an increased level of unpleasant adverse events (see page 32, lines 15-20). The table in Example 7 at page 32 of the specification clearly shows that undesirable adverse side effects, such as headache, dyspepsia, and back pain, are dose related; and an increase in adverse side effects with an increase in unit dose (doses from 25 mg to 100 mg). Also see specification, page 30, lines 15-23 and page 32.

The present specification further discloses "even though efficacy in the treatment of ED was observed at 25 mg to 100 mg unit doses, the adverse events observed from 25 mg to 100 mg dose must be considered," which indicates a dose above 20 mg (or above 25 mg) is not desirable due to an increased level of unwanted adverse side effects; in other words a higher dose above 20 mg would be less tolerable. Accordingly, the present invention teaches that a unit dose of about 1 to about 20 mg, about 2 to about 20 mg, and about 5 to about 20 mg of compound (I) is preferred.

Moreover, it has been recognized by the court that ranges which overlap or lie inside ranges disclosed by the prior art may be patentable if the applicant can show criticality in the claimed range by evidence of unexpected results. *In re Wertheim,* 191 U.S.P.Q. 90, 100 (CCPA 1976); and *In re Geisler.* As stated above, applicants showed the criticality of the claimed range by the evidence of unexpected and surprising results provided by the claimed dose range. This was further corroborated with the Declaration by Dr. Gregory D. Sides filed January 15, 2004. Moreover,

these findings of surprising and unexpected results are commensurate in scope with the claimed range. See *In re Greenfield*, 197 U.S.P.Q. 227, 230 (CCPA 1978) ("Moreover, the applicant's showing of unexpected result must be commensurate in scope with the claimed range.") Additionally, patentability is imparted in this case in view of the '329 patent because the results achieved at the claimed range are unexpected and surprisingly good as discussed above. See *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977).

The examiner stated in the Office Action that the first declaration of Dr. Sides is not persuasive because decreased side effects are expected at lower doses. Applicants respectfully submit that the examiner failed to appreciate the present invention as a whole. In particular, while decreasing a dose of drug often decreases side effects, it also often decreases efficacy. In contrast, the surprising and unexpected results of the present invention include at least two factors: the claimed unit dose range of about 1 to about 20 mg provides substantially decreased adverse side effects while still retaining efficacy. The observed divergence of retained efficacy from decreased side effects in these substantially lower doses is unexpected. It is not predictable that the low dose of about 1 to about 20 mg of Compound (I) would be efficacious. More significantly, it is neither expected from nor suggested by the '329 disclosure that the presently claimed low dose range of about 1 to about 20 mg would be efficacious as well as reduce the adverse events to such level that a patient suffering from erectile dysfunction would be treated effectively. In

other words, the '329 patent does not describe or forecast that a low dosage range of about 1 to about 20 mg would have the effects of efficacy *and* at the same time achieve unexpectedly low adverse side effects.

Therefore, in this case, patentability is imparted because the '329 patent fails to suggest to one of ordinary skilled in the art that the claimed range of the present invention should be carried out and would have likelihood of success. Moreover, the '329 patent disclosure of the broad range of 0.2-400 mg (in tablets or capsules) would not have suggested to one of ordinary skill in the art at the time invention was made that the low dose range of about 1 to about 20 mg would have unexpected surprising results of not only being efficacious but also having low adverse side effects as discussed above.

The examiner also stated in the Office Action that there is no showing of similar efficacy comparing 20 mg of the compound of the instant method with the 50 mg disclosed in the '329 patent. Applicants respectfully submit that the examiner's rejection based on this reason cannot be maintained. As stated above, the present application discloses efficacy data ranging from 2 mg to 100 mg. The examiner has not shown any rational and/or reasonable basis as to why a 20 mg would not be efficacious when the specification clearly discloses that doses below 20 mg and above 20 mg are efficacious (see page 31). One skilled in the art would understand that a 20 mg dose would be efficacious based on the clinical data disclosed in Example 7 of the specification. It is submitted that the examiner is requesting specific data without explaining why that

showing is necessary in this instance. However, in the interest of facilitating prosecution of this application toward a favorable decision, applicants herein file the Second Declaration by Dr. Gregory D. Sides, which shows that the efficacy of a 20 mg dose of Compound (I) is comparable to that of a 50 mg unit dose of Compound (I) in treating ED.

In view of the above, it is submitted that the present claims would not have been obvious over the '329 patent disclosure. Accordingly, applicants respectfully request that the rejection on this ground be withdrawn.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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